REMARKS

Claims 1-4, 11-14 and 16-24, 41, 42, 45, 47, 49, and 59 are pending in the application. Claims 19-21 and 47 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1-4, 11-14, 16-18, 22-24, 41, 42, 45, 49, and 59 are under active consideration.

Claims 3, 11, 12, 16, and 22 have been amended to depend from claim 1 or claim 2. Claim 45 has been amended to depend from claim 41 or 42. Entry of the amendments is respectfully requested.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 102(b).

Priority

The Office Action states that the subject matter of claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 16-18, 22-24, 41, 42, 45, 49, and 59 is not entitled to the benefit of priority of U.S. Application Serial No. 09/721,479 filed November 22, 2000 and provisional U.S. Application Serial No. 60/167,502 filed November 24, 1999. The Office Action asserts that the claims are drawn to a fusion protein comprising a modified NS3 polypeptide having an amino acid substitution that renders the protease of the fusion protein non-functional but that the specification of USSN 09/72,479 "...does not teach at least one amino acid substitution...[and thus] ...the earliest date to which Applicant may claim priority is July 2, 2002" (Final Office Action, page 2).

Applicants respectfully traverse this objection and the facts purported to underlie the objection for at least the following reasons. Applicants reiterate that provisional U.S. Application Serial No. 60/167,502 does describe "a mutant polypeptide, comprising at least portions of NS3, NS4, or NS5, comprising a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional" (see specification at page 11, lines 22-23). U.S. Application Serial No. 60/167,502 also states that a polypeptides may contain "one or more analogs of an amino acid" (see specification at page 16, lines 10-12). U.S. Application Serial No. 09/721,479 describes an HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3

that functionally disrupts the catalytic domain and states explicitly that "the mutation can be, for example, a deletion, or a substitution mutation" (see specification at page 4, lines 11-13). U.S. Application Serial No. 09/721,479 also describes analogs of polypeptides having one or more amino acid substitutions relative to the native molecule (see specification at page 12, lines 2-5).

For at least the foregoing reasons, Applicants respectfully submit that the invention as embodied in claim 1 is entitled to the benefit of the priority date of 09/721,479.

35 U.S.C. § 112, second paragraph

Claims 1-4, 11, 12, 16, 22, and 59 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Final Office Action, page 3). In particular, the Final Office Action alleges that the limitation in claim 1, "wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein" is unclear because "[t]he closed language of the preamble indicates that the fusion protein is made up only of the modified NS3 polypeptide and the non-NS3 polypeptide" and "[t]he new limitation indicates that there are possibly other sequences in the fusion protein" (Final Office Action, page 3). Applicants respectfully disagree and traverse the rejection.

Contrary to the Examiner's assertions, independent claims 1 and 59 use open claim language. In both claims, the preambles recite "an immunogenic fusion protein comprising." Thus, the claimed fusion proteins are not restricted to just two elements. In fact, part (b) of claims 1 and 59 makes explicit that a fusion protein comprises "at least one polypeptide from a region of the HCV polyprotein other than the NS3 region." That is, a fusion protein may comprise more than one sequence in addition to NS3.

Applicants submit that the phrase "comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein" is clear. One of skill in the art would understand this limitation to mean that the sequences in the fusion protein, which could include two or more, are not in the same order as they occur naturally in an HCV

polyprotein. Claims must be examined on the basis of whether one having ordinary skill in the art would be able to determine the scope of the claim and, if a rejection is made, reasons must be provided why the claim is indefinite. Applicants submit that the Examiner has not provided any reasons or evidence why the cited phrase is indefinite and/or why one having ordinary skill in the art could not determine the scope of the claims.

For at least these reasons, the rejection is improper and should be withdrawn.

35 U.S.C. § 103

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 16-18, 22-24, 41, 42, 45, 49, and 59 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Paliard et al. (WO 01/30812 A2; "Paliard") in view of the reference of Houghton et al. (U.S. 5,371,017; "Houghton") and Grakoui et al. (1993) J. Virology 67:2832-2843 ("Grakoui").

The presently pending claims are directed to immunogenic fusion proteins comprising a modified NS3 polypeptide comprising at least one amino acid substitution to the HCV NS3 region, such that protease activity is inhibited, and at least one polypeptide from a region of the HCV polyprotein other than the NS3 region, wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein.

All of the claims have been rejected as obvious in light of Paliard in view of Houghton and Grakoui since, according to the Examiner, it would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of Paliard. The Office Action concludes that:

> One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of polyprotein, as taught by Houghton (col. 3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function. (Final Office Action, page 6)

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 on the following grounds.

First, as indicated above, claim 1 is indeed entitled to the benefit of priority of USSN 09/721,479, filed November 22, 2000. Paliard was published May 3, 2001 and therefore is not a valid reference under 35 U.S.C. 103(a) as applied to claims 1 and 59.

Second, Applicants submit that there is no motivation in the cited references to combine these references and the Examiner has not pointed to any specific knowledge of facts that would lead to such motivation. Therefore, even assuming, arguendo, that Paliard is a valid 103(a) reference as applied to all of the claims, the combination of Paliard, Houghton and Grakoui do not render any of the other pending claims obvious, as detailed further below.

Paliard, the primary reference, discloses fusion proteins that are immunogenic. Paliard does not describe or suggest a fusion protein comprising an NS3 polypeptide modified such that protease activity is inhibited.

Grakoui describes mutation of the natural HCV polyprotein and in particular was cited for disclosing specific substitutions in the protease that result in uncleaved non-structural domains.

Houghton was cited by the Examiner for disclosing that certain substitutions result in the inhibition or ablation of protease function. Houghton discloses fusion proteins that comprise an "HCV protease, truncate, mutein or a functional portion thereof, fused to a non-HCV protein or polypeptide..." (see col. 6, lines 63-67; *emphasis added*).

Of the three references cited, only Paliard teaches the use of HCV fusion proteins as immunogenic compositions. Paliard, however, as noted by the Examiner, does not teach or suggest protease-inactive fusion proteins.

Grakoui pertains to the field of enzymology, and describes the use of site-directed mutagenesis to study proteolytic processing of the HCV polyprotein by the NS3 protease. Nowhere does Grakoui describe the use of these NS3 mutations for the preparation of immunogenic fusion proteins for eliciting an HCV immune response. Houghton also fails to teach or suggest fusion proteins comprising NS3 and other HCV polypeptides for use

as immunogenic compositions. Thus, Houghton also does not provide the motivation for mutating the protease activity of the fusion proteins of Paliard in order to provide an immunogenic fusion protein for eliciting an HCV immune response.

The Examiner is of the opinion that it would have been obvious to combine Houghton and Grakoui with Paliard because

> One would have had a reasonable expectation that Paliard's fusion protein **would have worked** with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity."
> (Final Office Action, page 6; *emphasis added*).

Since Grakoui and Houghton are both silent as to immunogenic compositions, there is no motivation to apply the NS3 amino acid substitutions or mutations taught in these references to an immunogenic fusion protein useful for eliciting an HCV-specific T-cell response, as described by Paliard. The Office cannot point to anything in Paliard that would motivate the skilled artisan to incorporate the protease-inactivating substitutions described by Grakoui and Houghton into the immunogenic fusion protein of Paliard. Nor can the Office point to Grakoui or Houghton for providing this motivation. Thus, no combination of the cited references provides the requisite motivation to combine the teachings to arrive at the claimed invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no

knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered

obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Michael J. Moran
Novartis Vaccines & Diagnostics, Inc.
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-2969
Fax: (510) 655-3542

Respectfully submitted,

Date: 5/25/06

By: _____
Roberta L. Robins
Registration No. 33,208

Novartis Vaccines & Diagnostics, Inc.
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097